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FUNCTIONAL ELECTRIC STIMULATION FOR SENSORY AND MOTOR FUNCTIONS: PROGRESS AND PROBLEMS

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Functional Electrical Stimulation (FES) endeavors to restore the lost functions of the nervous system by means of electrical stimulation. It is a multidisciplinary field on the interface between the neuroscience, engineering, rehabilitation and the clinic. In this review, the principal notions behind FES are outlined together with the relevant moments of its history. The specific research problems encountered in the development of FES applications are extensively covered. From an engineering perspective, special attention is dedicated to the electrodes for selective stimulation. The major clinical applications are overviewed: pacing of the heart, respiratory pacing of the diaphragm, cochlear neuroprostheses for restoration of hearing, the rehabilitation and restoration of locomotion and hand functions, and the restoration of bladder and bowel functions. An analysis of the current FES applications is performed from the perspective of the evidence-based clinical approach. Currently, FES for restoration of the lost locomotor functions is a rapidly developing area that is on the verge of broadening its acceptance in the clinic. Evidence for this is the increasing number of various neuroprosthetic devices, some of them already beyond the prototype stage, that have been developed recently. The present FES treatments combined with conventional occupational and physical therapy still remain the most promising approach in rehabilitation of the spinal cord injury patients and the stroke patients. FES in combination with neuromodulation, which is however still in a rather empirical state of operation, becomes a viable option in the treatment of various urological disorders. The analysis indicates that the pacing of the heart and cochlear neuroprostheses remain the most developed applications of FES. The presented overview of the FES applications shows that a number of fundamental scientific problems have to be solved before a comparable degree of effectiveness and penetration in the common medical practice is achieved for the locomotion neuroprostheses and the urological FES appliances. Finally, a summary is given of the major clinical and fundamental directions of research needed for further improvement of FES.
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INTRODUCTION - HISTORY OF ELECTRICAL STIMULATION

Functional electrical stimulation (FES) is a part of the broader field of electrotherapy. The term was introduced relatively late in the history of FES by Moe and Post (1). The history of electrical stimulation follows the theoretical and technological breakthroughs in the study of electricity and magnetism together with the developments in Neuroanatomy and Neurophysiology, since the stimulation is mainly an application of electro-magnetic theory in the nervous system. Nevertheless, the history of electrical stimulation has its own milestones of which the major ones, related to the nervous system, are given in this review.

In the field of Neuroanatomy, the application of ethanol

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to fix brain tissue (Felix Vicq d'Azyr, 1748-1794) opened the microscopic approach for the study of the brain, ending up with the detection of the subcellular protrusions of the neuron and its supporting cells. One should notice that the detection of the microarchitecture of peripheral nerves (Van Leeuwenhoek, 1719) was remarkably accurate but forgotten for nearly a century. The descriptions of Dutrochet in 1824 (2) and Remak in 1838 (3) once again depicted the tubular structure of the entities in the nerve, together with the detection of myelinated and non-myelinated fibers.

Albrecht Haller (1708-1777) described the "irritation phenomenon of muscles", in fact the contraction and relaxation of muscle. In his notion, it was a "force" that passed along the nerves that could induce this excitation of the muscles. In addition, Haller made the first concept on sensibility. He found that tissues by themselves lack sensations, but the latter were perceived and relayed by the nerves and their endings.

Luigi Galvani (1737-1798), after extensive studies of the muscle contractions in cadavers, developed the theory of the "animal electricity" - an electric fluid contained in the nerves, which caused contractions of muscles. Later on in 1792, Allesandro Volta (1745-1827), who developed the so-called "galvanic" element, could demonstrate that the galvanic element used electricity. These theories bridged Neuroanatomy-Neurophysiology and the study of electricity, so that the nerves could be regarded as the electric cabling of the body (Fig. 1).

In the meantime, friction electricity was in use and the first capacitor, "de Leidse fles" (1746), was developed by Muschenbroeck. From 1784 to 1791 the biggest friction-electrical machine was build by John Cuthbertson. Van Marum (1750-1837), biologist, physician and botanist, used this machine to do electrophysiological research for ten years. This shows that around the beginning of the XIX century systematic application of electricity in research and medicine had already started (Fig. 2).

By the middle of the XIX century with the discovery of static electricity, capacitance and electromagnetic induction, physiologists could study muscle contractions, nerve conduction and cell excitation. J.Müller (1801-1858) introduced

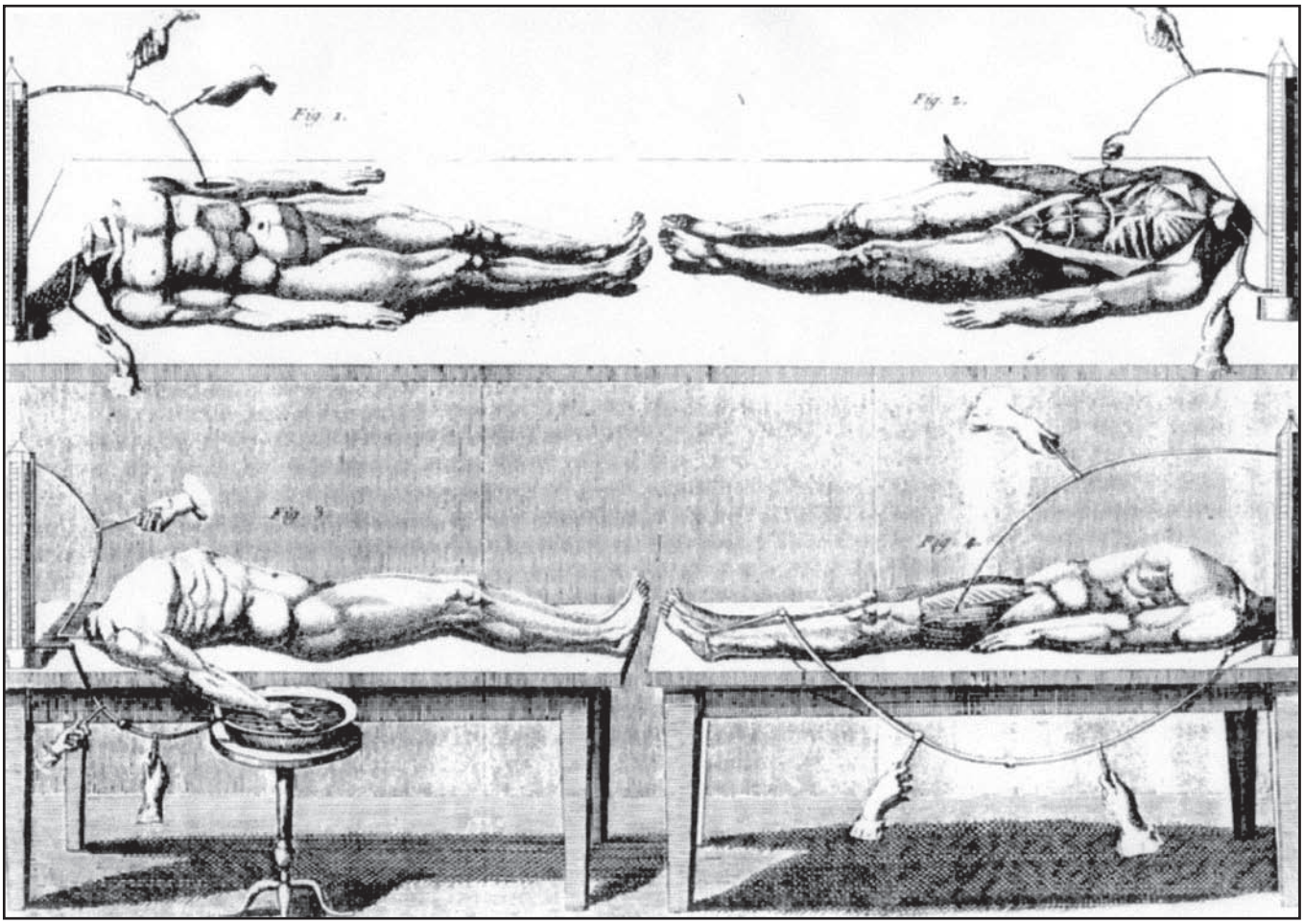

Figure 1. *The experiments of Luigi Galvani on human muscles: muscles of a cadaver contracted when a metal object closed the loop with a nerve. From G. Aldini, Essai théorique en experimental sur le Galvanisme, avec série d'experiences... Paris, Fournier fils, 1804. Courtesy: Prof. H. Beukers, Leiden University.*

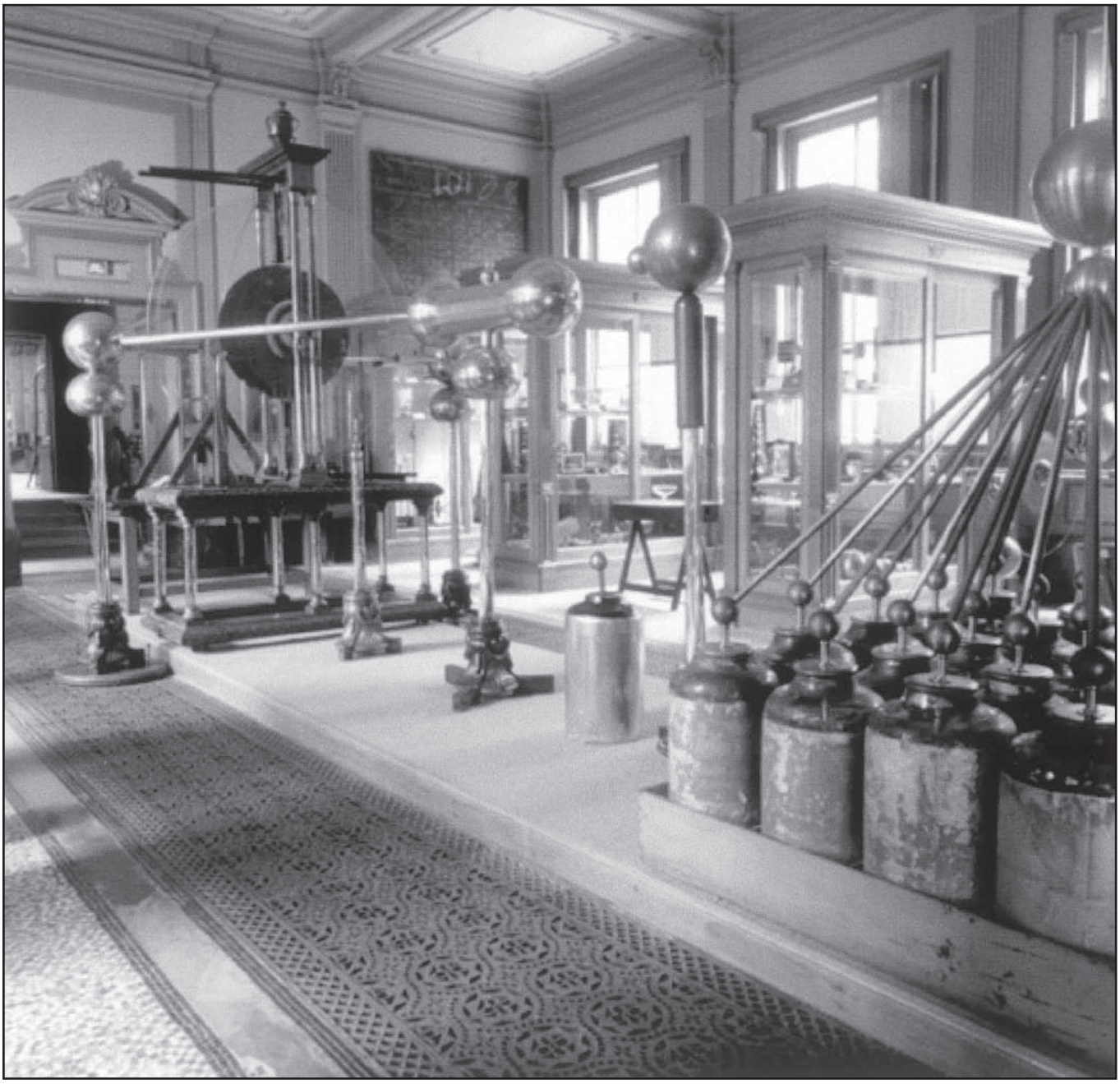

Figure 2. *The enormous friction electrical machine together with the Leiden jars built by J. Cuthbertson. Courtesy: Teylers Museum. For its operation, two men had to move two enormous glass discs. Each disc was frictioned by four cushions. The electricity on the glass discs had to be induced into the conductors by an array of Leiden jars. The potential difference reached nearly 330 kV.*

the Law of Specific Nerve Energies which stated: "the kind of sensation, following the stimulation of a sensory nerve, depends not on the mode of stimulation but on the nature of the sense organ with which the nerve is linked". His own disciple Helmholtz (1821-1894) measured the velocity of the nervous impulse and Emil DuBois-Reymond (1818-1896), also a disciple of Müller, proved the existence of the resting membrane potential in the nerve fibers and also proved that each impulse is directly related to a change in potentials. Sir Charles Bell (1774-1842) and Francois Magendie (1783-1855) established the neuronal basis for the reflex. The dorsal roots relay afferent, sensory information, while the ventral root controls the motor function.

The final idea that the central nervous system is the controller of the organism was brought forward by T. H. Huxley (1825-1895) in his *Manual of the Anatomy of the Inverte-*

brate Animals (1817) and became generally accepted. This concept became the fundament for the effective application of electrical stimulation. In this period, medical applications were numerous but short lived and poorly understood. Electricity was reported to cure rheumatism, neuralgia, insomnia and even cold feet (4).

In XX century, the major technological advances in electronics and computing (the discoveries of the diode, triode, transistor and integrated circuits) lead to the development of contemporary FES appliances. The main push in the applications of FES was the successful development and clinical applications of the heart pacemakers.

Literature shows controversy about who was the first inventor of the artificial heart pacemaker (5). In 1932 Albert Hyman described an "artificial pacemaker" that he had used with experimental animals to resuscitate the "arrested" heart. About that time, the Australian physician Mark C. Lidwill, along with the physicist Major Edgar Booth, built a portable pacemaking unit. It was demonstrated in 1931, while Hyman developed his device in 1930-31. Lidwill's apparatus had one pole applied to the skin and another into the appropriate cardiac chamber (6). Later on, the Hyman device was successfully used in patients.

The application of cardiac pacemakers to stimulate the human heart dates as far back as 1954. However, it was not until the 1960s when pacemakers were adopted on a large scale in clinical practice. In the beginning, their potential for different applications was not recognized by both the medical society and the industry. Another reason was the immaturity of the technology and the implantation techniques. Stimulation was carried out by skin electrodes, which left uncomfortable burns when used for more than a couple of days. Later, electrode wires leading through the skin were tried, but infections along the wires were an unsolvable problem (6). This could be circumvented by the implantation of the entire pacemaker. Rune Elmqvist designed the world's first implantable pacemaker. The first 10 patients for the implantable pacemaker were operated in 1960 (7). In the 1970s, heart pacemakers demonstrated the reliability of implanted electronic devices and showed the benefits in terms of improved quality of life.

In parallel to the development of cardiac pacemakers went the attempts to apply stimulation of the diaphragm for respiratory pacing. For some 200 years, electricity has been applied to the phrenic nerves to activate the diaphragm. However, the actual therapeutic opportunity arose in the 1950s, by the time the heart pacemakers were developed. The first attempts to pace the diaphragm with implanted electrodes were carried out between 1948 and 1950 by Sarnoff and coworkers (8). One of the most important prerequisites of the routine clinical applications was the introduction of the long-term electrical stimulation by the radio frequency inductive method introduced around the end of the 1950s (9). In 1966, Dr William Glenn at Yale University, USA, performed the first clinical application to patients with hypoventilation of central origin. The ventilation support was made by radio frequency pacing of the diaphragm. Pacing for total ventilatory support in patients with respiratory paralysis was applied in 1971. In the early 1980s the first commercial phrenic nerve pacers were introduced. As a result of the successful application of the pacing of the heart, the technological advances achieved during the development of the pacemakers were also successfully applied in other neural prostheses. Restoration of hearing to the profoundly deaf was an early target.

A report by Gersuni and Volokhov in 1936 (10) indicated that hearing could be produced over a normal frequency range, and that it persisted following the surgical removal of the tympanic membrane and ossicles. One of the first recorded attempts to stimulate the auditory nerve was made by Lundberg in 1950, who employed sinusoidal currents during a neurosurgical operation. The patient could only hear noise. However, a milestone for the development of the auditory prosthesis was the electrical stimulation of the acoustic nerve of a deaf man by an implanted electrode achieved by Djourno and Eyries (11). They used an implanted induction coil connected with one end to the inner ear electrode and with the other to an indifferent electrode at the temporal muscle. Another coil, outside the body, was held over the implanted coil to inductively transmit the signal from a microphone. The usefulness of the device was very limited since the patient could recognize only few words from the transmitted signal. This operation, however, opened the doors for further attempts to interface the sense organs.

The early investigators were subjected to severe criticism by both neuroscientists and clinical professionals for the insufficient safety studies and unsatisfactory design of the implants used. The safety of the cochlear implantation improved in the late 1950s with the evolution and developments of microsurgical techniques and stapes surgery. The indications and contraindications for this implantation were elaborated in a broad debate between the clinicians and the promoters of the cochlear prostheses. Questions were also raised about which device should be used and about the safety of the electrical stimulation. The 1970s could be considered as a decade of controversy concerning the implant itself and its use. Finally, after more than twenty years of ongoing experimentation, in 1984 the cochlear implant received FDA approval for use in adults in USA. Nowadays, the cochlear implant is a historical example of how a neural prosthesis can revolutionize treatment.

In 1929, Foerster described the effects of electrical stimulation of the human visual cortex (12). The subjects reported for "perception" of a small point of light during stimulation, which was later called a phosphene. This result was reproduced many times in both sighted and blind subjects. The

idea that concurrent stimulation of many sites in the brain could produce a single coherent image was postulated by Krieg (13), based on the retinotopy in the visual cortex.

As a second milestone for the development of neural prostheses can be accounted the implantation of prosthesis in the visual cortex of a blind woman in 1968 by Lewin and Brindley (14). The prosthesis did not benefit the patient much (she reported only about occasional phosphenes in her visual field), but demonstrated that it is possible to transfer large amount of information in the visual system. Giles Brindley, one of the greatest protagonists in the FES field, attained recognition and acceptance of the applications of neural prostheses in the clinical field. The results obtained by the Brindley implant and the early cochlear stimulator showed the need to stimulate selectively small groups of neurons or fibers in order to transmit meaningful information into the central nervous system.

Attempts to restore the lost functions of the paralyzed leg muscles were performed for the first time in 1961 by Liberson and colleagues (15). The system was developed to compensate for the "drop foot" problem in hemiplegic stroke patients. By stimulating the peroneal nerve, the prosthesis triggered ankle dorsiflexion, eversion and inversion. Since 1961, a number of neuroprostheses for restoration of walking, hand and arm functions have been designed and tested with various patients and with different levels of success.

Apart from these well-endorsed success stories, other applications of FES still suffer from major difficulties regarding the clinical acceptance and patient compliance. Two examples are given here. Long and Masciarelli introduced prosthesis for the hand that could not meet the expectations of the patients and it was later on abandoned. In the 1970s, attempts to treat refractory epilepsy were also carried out by means of stimulation of the cerebellar cortex. Later on, the performed double blind clinical trials did not confirm the claimed effects (16).

In conclusion, the history of FES shows that pacing of the heart emerged at different places and its success stimulated pacing of the diaphragm. The criticism of the early cochlear prostheses could be surmounted by tenacious research. However, one may consider these first successful applications as "lucky shots", based on the simple reactions of the involved organs: for the cardiac muscle and the diaphragm - simple contraction, and for the inner ear - linear tonotopical organization allowing simple encoding of the stimulating signal. Neuroprostheses for locomotion as well as those for reaching and grasping, on the other hand, require selective stimulation of the fibers in the nerves, which innervate the muscles making the movements. Therefore, in the case of selective nerve stimulation, the research should be directed towards localization of the types of (myelinated) axons and their spatial organization.

Like the clinically recognized "success stories" of electrical stimulation, FES for restoration of the lost locomotor functions is a rapidly developing area that is on the verge of broadening its applications. Evidence for this is the increasing number of various neuroprosthetic devices that have been developed recently. Some of them are already beyond the prototype stage. That is why this paper will deal further on primarily with the electrical stimulation of the motor system.

PRINCIPAL NOTIONS IN FES

FES aims at restoring the lost functions of the nervous system by means of *electrical stimulation*. This can be achieved by either rehabilitation thus improving recovery or by *prosthesis* (artificial substitution of a dysfunctional part) of the lost function or *orthosis* (device around organs in the case of impairment) of the diminished function. Example of the latter is the peroneal stimulator for foot-drop, and of the former - the stimulators of the phrenic nerve. FES is also sometimes referred to as Functional Neuromuscular Stimulation or FNS. This approach is limited only to the sensory and the motor functions. The initiation of reflex activity is, though, not the aim of FES but may be a secondary useful collateral effect.

Electrochemical processes at the tissue-electrode interface

Electrical stimulation of biological tissues with metal electrodes requires the flow of ionic charge in the biological tissue. This flow is induced by both capacitive and faradic mechanisms. The capacitive mechanism involves periodic charge and discharge of the electrode double layer. There is no charge transfer across the electrode/electrolyte interface. This is an ideal mechanism for charge injection, but it is limited by the maximal amount of charge that can be transferred before the dielectric breaks down. It is approximately 20 μC/cm^2. Because the charge required for physiological stimulation exceeds this limit, all electrical stimulation is performed by faradic charge injection. The faradic mechanism involves charge transfer across the electrode/tissue interface and, therefore, electrochemical reduction/oxidation processes. These reactions can be either reversible or irreversible. All irreversible electrochemical reactions are undesirable since they alter the chemical composition of the extracellular fluid, producing cytotoxic products or bringing about large changes in pH. For every material used in the production of electrodes, there is a charge limit for the reversibility of the electrochemical process. The charge limit depends on the properties of the material, the shape of the electrode, its size, and the stimulation waveform. According to Robblee and Rose (17), the temporal shape of the stimulation wave is the most important.

In order to diminish the oxidation and dissolution of the electrodes, generally a noble metal like Pt, Ir or Au is used as a material for the anode. Of the non-noble metals, 316L stainless steel is also used for intramuscular electrodes (18). At the cathode, however, O_2 molecules are reduced to O_2^-, which in turn react to produce free radicals. The free radicals are known to damage the cell membranes and DNA molecules. During a typical neurostimulation pulse, a substantial amount of the O_2 molecules is reduced to anions (19). Part of the free radicals generated near the cathode can be neutralized by oxidation when an anodic pulse follows the cathodic pulse. Morton *et al* (19) concluded that the reduction of oxygen, and thus the generation of free radicals, are most restricted when the cathodic pulse has a small width and when an anodic pulse with the same charge immediately follows the cathodic pulse. This principle is known as *biphasic charge-balanced stimulation* (20). The continuous stimulation by biphasic, charge-balanced pulses without delay between the pulses is more beneficial with regard to nerve degeneration than stimulation by pulses with delay (21). The continuous stimulation by biphasic, charge-balanced pulses was shown not to have harmful effects on sciatic nerves (22).

Voltage-controlled and current-controlled stimulation

Historically, the implantable FES systems in clinical applications have generally been voltage-controlled, as for example are cardiac pacemakers. In contrast, the current-controlled devices dominate in experimental setups. In the voltage-controlled devices, the output voltage **V** of the pulse generator is regulated. Generally, **V** is kept constant, thus creating a rectangular voltage pulse, the related current obeying Ohm's Law. In contrast, in the current-controlled devices the current **I** is kept constant, whereas **V** is automatically adapted according to the value of the impedance **Z**, which may vary over time due to the reaction of the surrounding tissue to the implant. The current needed for stimulation does not change chronically and thus no corrections are needed. In the voltage-controlled systems, however, the voltage needed for stimulation is influenced by the changing value of **Z** over time and thus the amplitude of stimulation has to be adapted at least in the first two months after implantation when the fibrous encapsulation layer develops. Since the current consumption determines battery life of an implanted pulse generator, it is important that the stimulation current is determined in the first place. This is, however, not possible when a voltage- controlled pulse generator is used, as **I** depends on the unknown value of **Z**. Therefore, the battery life cannot be accurately predicted from **V**. Nevertheless, it is often erroneously assumed that a reduction of **V** reflects a reduction of **I** and *vice versa*.

Monopolar, bipolar and tripolar stimulation

Since the cathodic threshold for nerve fibers is 3-7 times lower than the anodic threshold current, cathodic stimulation is by far the most efficient way (23). In monopolar stimulation, the active electrode (in or near the neuronal target) is therefore the cathode and the distant, indifferent electrode, is an anode. In that situation, the current injected by the cathode is distributed more or less evenly in all directions. Activation of nerve fibers always happens near a cathode in bi-, tri- and multipolar stimulation. For the optimal stimulation, in bi-, tri- and multipolar stimulation, the position of the cathode is more important then the position of the anode. In the clinical applications of FES phenomena such as cathodic block, anodic excitation and anodic block are not likely to occur (24,25). The threshold current for stimulation of a nerve fiber increases with the distance between the cathode and the fiber and is inversely related to the fiber diameter. The preferential stimulation of large fibers is favored most when short pulses (~ 60 ms) are applied. Smaller fibers can be activated more easily when pulses are wider. The current consumption is minimized when stimulation is given with a "guarded" cathode parallel to the fiber bundle as in peripheral nerve stimulation and Spinal Cord Stimulation (SCS).

Cable properties of the nerve fibers

The theory of the current flow in electric cables was developed for submarine cables by Lord Kelvin (1855). For the first time it was applied in studies on excitable cells towards the end of XIX century. Cable theory opens the possibility to derive equations for current flow in cylindrical nerve and muscle fibers subjected to voltage changes which are small enough for the membrane properties to be linear; or equations that describe finite cables, since in most experiments the length of the preparation is not large enough, compared to the space constant λ for the cable regarded as infinite. This means that the behavior of the impulse in an axon can be predicted.

Active properties of the nerve fibers

The nerve fibers conduct information by means of action potentials propagating at a velocity proportional to the fiber diameter (Table 1). Moreover, the threshold of excitations also depends of the fiber type. In the myelinated fibers, the conduction is saltatory, with the active involvement of the nodes of Ranvier. For the first time the action potential of the non-myelinated fibers were mathematically described by Hodgkin and Huxley in 1952 (26).

The electrical behavior of the myelinated nerve fiber can be represented by a simple cable network (Fig. 3). McNeal was the first to introduce this model (27) in order to calculate how a stimulation-induced extracellular field affects nodal transmembrane voltages. According to this model, the node

Table 1. *Morphological and electrophysiological features of the fibers in peripheral nervous system*

Fiber type	Class	MCV[1] (m/s)	Diameter (μm)	Function
Aα	myelinated	70-120	12-20	motor somatic muscle fiber, proprioception, muscle spindle annulospiral, proprioception, Golgi tendon organ
Aβ	myelinated	70-120	5-12	proprioception, muscle spindle flower spray, exteroception, touch and pressure
Aγ	myelinated	30-70	3-6	motor somatic muscle spindle
Aδ	myelinated	12-30	2-5	exteroception, pain temperature (some) touch
B	thin myelinated	3-14	<3	motor, autonomic preganglionic
C	unmyelinated	0.5-2.5	0.4-1.2	exteroception, pain reflex responses
C	unmyelinated	0.5-2.5	0.3-1.3	motor, autonomic postganglionic

[1]Mean Conduction Velocity

of Ranvier that is closest to the cathode will be excited first when the stimulus current is sufficiently high. The results of this theoretical approach are in accordance with the general observation that the threshold stimulus of nerve fiber excitation is smallest near the cathode and rises with the increase of the distance (23). As a result, cathodic stimulation gives rise to a depolarization of several nodes, whereas a larger number on both sides of the cathode are hyperpolarized to a lesser extent, thus creating a virtual anode.

In anodic stimulation the opposite effects occur. The *virtual anode* and *virtual cathode* effects underlay phenomena such as cathodic block and anodic excitation. Anodic excitation is possible when the anodic current is so large that the virtual cathodic depolarization on either side of the hyperpolarized membrane generates action potential. In cathodic block, the opposite is true - if the cathodic current is large enough the induced virtual anodic hyperpolarizations can block the propagating action potential. The McNeal model is the basis of all the theoretical research performed in the area of FES.

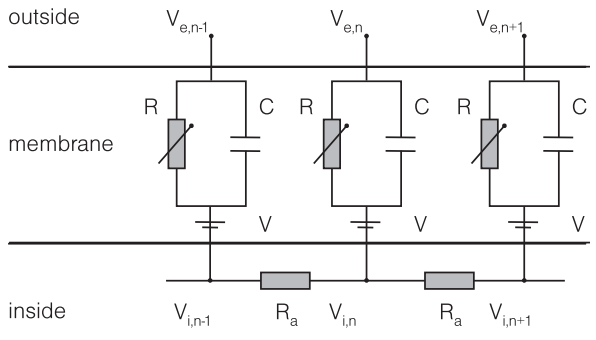

Figure 3. *The McNeal cable model for the axon. Each node of Ranivier is represented by an equivalent electric scheme. Vi - intramembrane potential, Ve - extramembrane potential, Ra - intraaxonal resistance, R - variable membrane resistance, C - membrane capacity, V - resting membrane potential.*

Stimulation Electrodes

Spatially selective stimulation of the nerve fibers within a given nerve bundle is important, because different muscles are innervated by fibers having a specific localization within a nerve bundle, and moreover often a mixture of efferent and afferent fibers is present in the nerve. Such mixed populations may lead to undesirable sensations during stimulation. In the case of several nerve fibers innervating different muscle fibers of one muscle, cyclic stimulation can be performed which guarantees an overall stimulation frequency, while stimulation frequency and thus fatigue of a single muscle fiber can be kept low (28).

There are many different designs of electrodes employing different materials and geometries of the contacts. Most of them are used only in animal experiments, and only few are also employed in clinical FES applications. A simple classification of the FES electrodes follows: (*i*) surface (skin) electrodes; (*ii*) intramuscular and epimysial electrodes; (*iii*) extraneural electrodes (cuff or helical electrode around a peripheral nerve); (*iv*) intraneural wire electrodes; (*v*) intraneural linear, 2D and 3D multi-electrode arrays. An extensive

account on the cuff, intrafascicular and sieve electrodes designs and fabrication technology can be found in (29) and (30).

• *Surface electrodes*

Transcutaneous stimulation is performed with self-adhesive or non-adhesive electrodes that are placed on the subject's skin, above the peripheral nerve (respectively the motor fibers). The metal electrode is connected to the skin with a saline bridge. Desired features for surface electrodes are low impedance with even current spread, flexibility, ease of application, and removal, and lack of skin irritation (31). The application is simple. Nevertheless, damage of the skin only can occur by the diffusion of soluble electrochemical products. The large distances to the stimulation targets and the insulation of the skin and the fat tissue demand high stimulation strengths, which in turn results in low selectivity. Complications are rare and include burns, skin irritation, erythema and local pain.

• *Intramuscular and epimysial electrodes*

Muscle electrodes have their stimulating surfaces onto or inside a striated muscle. In the former case, they are sutured to the epimysium of the muscle and are therefore called epimysial. If terminal motor branches are present, the electrodes exert their action by stimulating the nerve endings. Therefore, they can be considered also as nerve electrodes. In comparison with the transcutaneous electrodes, they produce contractions with lower currents and with greater selectivity. For these reasons, muscle-based electrodes are preferable for situations that require independent control of several isolated muscles. Depending on their intended application, the intramuscular electrodes can be introduced either percutaneously (e.g. 32) or in an open surgical procedure (33). However, the intramuscular electrodes can also activate neural structures near their stimulating tips other than those intended, thus recruiting muscles in addition to the ones targeted (34). Nevertheless, these electrodes are considered safe and effective means to produce strong and isolated contractions of single muscles. Complications include infections and wire breakdowns. In an effort to avoid the use of percuataneous leads for muscle electrodes, Loeb (35) and Cameron *et al* (36) developed implantable muscle stimulators that can be controlled telemetrically, and are inductively powered from external magnetic devices in order to overcome infections. According to the promoters of this approach, this would ultimately alleviate the burdens involved with maintenance of the awkward external electronic equipment.

• *Cuff electrodes*

Cuff electrodes circumscribe the nerve (Fig. 4). They were introduced in the 1970s. The first cuff electrodes had a very simple cylindrical rigid design. Modern cuff electrodes use

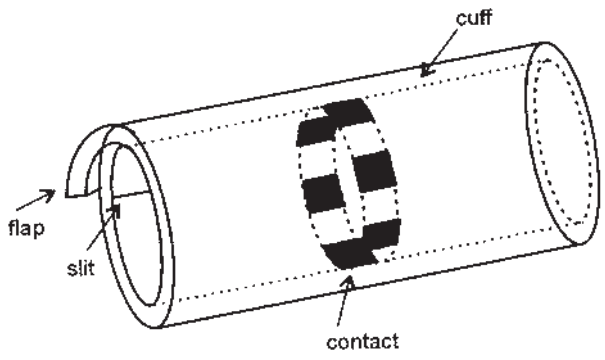

Figure 4. *A schematic view of a cuff electrode. Courtesy: K. Deurloo, from (96).*

flexible materials and adaptable geometries. They are implanted by a simple surgical procedure, and their size can be adapted to the diameter of the nerve of interest. If needed, they can be surgically fixed to adjacent tissues. Various designs have been developed and applied such as the helix-shaped electrode (37), the spiral-cuff (38), and the so-called "half-cuff" electrode (39). Another particular design is the arrangement of flexible interdigitating subunits with microelectrodes along a backbone-like carrier (40). The main push for their continuing development was the inadequate spatial and fiber selectivity they provided at first. The first cuff electrodes could stimulate only the most superficial fibers of the nerves (29).

With a sufficient number of electrodes within the cuff, high spatial selectivity of stimulation can be achieved by combinations of longitudinal and transversal currents produced by appropriately switched electrodes (41). Longitudinally aligned tripolar dot electrodes on the surface of a nerve trunk restrict excitation to superficial nerve trunk regions more successfully than monopolar dot electrodes (42). Selectivity was dependent on the relative location of the electrode contacts and the nerve fascicles, as well as the size and relative spacing of neighboring fascicles of a 12 contact spiral nerve cuff electrode (43). On the basis of computer modeling results, Deurloo *et al* (44) concluded that transverse steering provides better selective stimulation than longitudinal steering. However, the fiber size selectivity problem during stimulation could not be solved by these methods. Goodall *et al* found that large fibers were activated before smaller with a cuff electrode containing 12 electrodes arranged in four longitudinal tripoles, irrespective of the fiber position (45). Transverse current from an anode positioned opposite to the stimulating cathode was found to improve spatial selectivity, and position selectivity was enhanced when the ratio of transverse current to longitudinal current was increased. The use of silicone and helical designs in cuff electrodes has improved

surgical access and reduced nerve damage (41,46,47).

In an attempt to overcome the selectivity problems occuring in cuff electrodes stimulation, *intraneural* electrodes that directly contact nerve fibers within a given nerve bundle were developed.

• *Intraneural wire electrodes*

Intraneural wire electrodes are also referred to as penetrating electrodes. The first penetrating electrodes were simply thin metal wires or needles, which were inserted into the nervous tissue. They are used for both recording and stimulation. An interesting, non-silicon approach for intrafascicular stimulation is the use of tethered platinum microwires. Nannini and Horch (48) tested the performance of Pt-Ir intrafasicular electrodes (25 µm diameter) implanted in nerves innervating the gastrocnemius and soleus muscles. Originally developed for recording purposes, these electrodes proved potentially suitable also for FES. Yoshida and Horch (49) used dual intrafascicular electrodes to study activation of nerve fibers by pairs of Pt-Ir wire electrodes implanted within single fascicles of the nerve innervating the gastrocnemius muscle in cats. They aimed to determine whether intrafascicular electrodes can activate nerve fibers in different fascicles independently of each other, and if they can be used to activate separate subsets of axonal populations within a single fascicle.

• *Intraneural multi-electrode arrays (MEAs)*

MEAs can be classified into linear multielectrodes, two-dimensional (2D) arrays, and three-dimensional (3D) arrays. Linear multielectrodes are 1D- arrays consisting of wedge-shaped microprobes carrying single lines of electrode sites for recording and stimulation (50). The 2D-array consists of electrodes with tips ending in the same plane. The tips are configured either as a bundle of wires or galvanically grown needles. The substrate carrying the electrodes is either needle- or wedge-shaped in order to allow penetration of the nervous tissue which makes recording from and stimulation of axons possible not only on the surface but also in a well-defined depth within the tissue, e.g. within the fiber bundle. When the array is slanted or the needles have otherwise variable lengths, the electrode is named a 3D-array. Implantation of any such a device is always associated with some damage of the nervous tissue, cell death of neurons and disruption of axons. Moreover, stiffness of many models may also lead to mechanical damage of nervous tissue. Thus, the efforts are directed to miniaturize the penetrating parts of the implant and to use materials that are more flexible. Rutten *et al* (51) produced a 3D needle array with 128 recording sites on one electrode placed on the tip of a needle (see Fig. 5). The needles are made of silicon and are embedded into a glass substrate. They vary in height from 250 to 600 µm and have a distance of 120 µm, with a tip size of 15x15 µm. The array is intended to serve as an interface between a stimulator and a peripheral nerve. The different length of the needles allows stimulation in the volume of the nervous tissue. The dimensions of the array were based on calculations for optimal stimulation, based on random uniform distribution of the nodes of Ranvier in the peripheral myelinated axons.

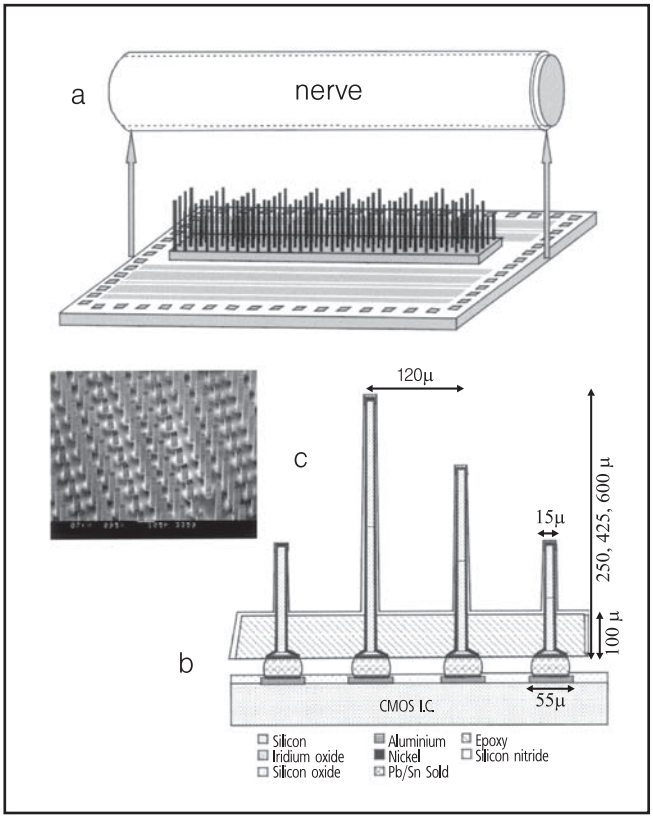

Figure 5. (a) *Scheme of the University of Twente 128-electrode 3D glass-silicon array (UT-128 array), mounted on a CMOS, mixed mode, processing chip with dimensions 4x4 mm. Needle lengths are 600, 425 or 250 µm, width at tip is 15µm, needle spacing is 120 µm.* ***(b)*** *Details of the dimensions and materials used for the UT-128 array.* ***(c)*** *A 'sea' of sawn and etched silicon needles of three different lengths, embedded in a glass matrix. Courtesy: W. Rutten, from (30).*

For signal recording and stimulation over a larger area, e.g. areas of the cortex, 2D MEAs are necessary. An example of such a 2D array is the Utah Electrode Array initially developed by Nordhausen and colleagues (52). It is designed for implantation in the human visual cortex and is intended as prototype in development of visual prostheses (53). It provides a multichannel interface to the visual cortex using a large number of 1.5mm long electrodes (typically 100 in a 10 x 10 square grid) projecting out from a very thin (200 µm) substrate and are separated from each other by 400 µm.

With the technological advance in the field of constructing flexible polymeric substrates, the so-called "flexible nerve

plates" came into development (54). They consist of a flexible substrate, which carries a microelectrode array and it is possible to add other elements of a microelectronic circuitry. In general, the silicon microtechnology based fabrication leads to improvement of recording structures, which made possible to create not only planar 2D microelectrode arrays, but also intraneural electrode structures for *in vivo* measurements. Alike the cuff electrodes, geometry and arrangement of the intraneural electrode arrays are currently optimized to fit with geometrical nerve fiber characteristics (fiber position in a bundle, diameter of the fibres and their orientation). While Smit (55) argues for intrafascicular stimulation, the proposed approach could be employed only in acute experiments, thus limiting the use of the obtained knowledge for clinical applications.

In theory, the intraneural electrodes should give a better spatial selectivity than the cuff electrodes (49,56). However, the random distribution of the nodes of Ranvier in the peripheral nerves makes the stimulation a probabilistic process. The implanted intraneural electrode may simply miss the target fiber population when the topography of the nerve fibers is unknown. Further, since during implantation these intraneural electrodes must penetrate the relatively tough epineurium and the perineurium of the nerve, they can cause short- and long-term nerve damage during the electrode insertion procedure (57-60). Nevertheless, histological results suggest that intraneural electrodes can be used chronically in peripheral nerves (60-62). Moreover, a really reliable fixation of the cuff must be achieved because otherwise the cuff may rotate around the nerve or shift along the nerve, both leading to a serious loss of selectivity.

To summarize, the implantable electrodes are surgically set in around, within or adjacent to a nerve trunk or root. By means of transcutaneous electrodes it is difficult or impossible to selectively activate individual muscles, especially deep muscles such as hip flexors (64,65). Large currents may be required to drive sufficient charge through the skin and intervening tissues between the electrode and the peripheral nerve. In many cases, cutaneous pain receptors are excited, and patients with preserved or heightened sensation may find it difficult to tolerate surface stimulation at the levels required to produce a functional motor response.

Advantages of the implantable electrodes over the superficial, epimysial and intramuscular include:

1. The current needed to excite an action potential in the target fibers is smaller at least an order of magnitude than the current required for the latter designs.
2. Muscle length and limb position are expected to have substantially less effect on the recruitment characteristics in the case of an implantable electrode.

Cuff electrodes are easy to implant and are generally less invasive to the nerve than intraneural electrodes are. Despite all new developments in electrodes, the robustness of stimulation is hampered by the structure of the nerve: the random distribution of the nodes of Raniver, and the fasciculation, typically present in the nerve. The main prerequisite for successful application of the modern sophisticated electrode designs and stimulation protocols is detailed knowledge of the topography of the nerve fibers within the nerve bundle and their function. An ideal peripheral nerve electrode array should have the neural selectivity of the intraneural electrode and the ease of implantation, stability, and biocompatibility of the extraneural electrode.

RESEARCH PROBLEMS

The major issues in the development of a neural prosthesis from the neuroscientist's point of view are (*i*) biocompatibility of the materials, which determines the long-term use of the device; (*ii*) detailed neuroanatomical and neurophysiological knowledge of the system, which in the end determines the effectiveness of the device.

Biocompatibility of the implantable devices: general considerations

Implantable devices should be able to survive in the rather aggressive internal milieu of the body without causing significant tissue reaction. The major prerequisite for the application of implants is that the organism accepts the implant, i.e. that the implant is biocompatible. This also holds for objects that come in close contact with the skin or mucose. An accepted definition of biocompatibility is "the ability of a material to perform with an appropriate host response in a specific application" (66). The selection and evaluation of materials and devices intended for use in humans requires a structured program of assessment to establish biocompatibility and safety. The current regulations, whether in accordance with the US Food and Drug Administration (FDA) (ISO 10993-1/EN 30993 standard, since 1995), the International Organization for Standardization (ISO), or EU regulation bodies (EU council directive - 93/42/EEC, since 1993), require conduction of adequate safety testing of the finished devices through pre-clinical and clinical phases as part of the regulatory clearance process (67). An extensive account on the biocompatibility may be found in the standard ISO 10993-1/EN 30993.

In brief, the notion of biocompatibility encloses non-toxicity, non-immunogenity, non-carcinogenicity, non-mutagenity and hemocompatibility. An implant can be considered biocompatible if it gives negative results on the following tests: *(i) Cytotoxicity; (ii) Sensitisation; (iii) Genotoxicity; (iv) Implantation; (v) Chronic toxicity; (vi) Carcinogenicity; (vii) Intracutaneous irritation; (viii) Acute systemic toxicity; (ix) Subchronic toxicity.*

According to Heiduschka and Thanos (29), the "biosafety" and the "biofunctionality" also have to be considered. Biosafety means that the implant does not harm its host in any way, and biofunctionality means that the implant acts in the body as it was intended. In addition, "biostability" is important which means that the implant must not be susceptible to attack of biological fluids, proteases, macrophages or any metabolic substances. For example, implants may be subject to continuous attack by hydrolytic enzymes (68) or free radicals produced by monocytes and/or cell lysis. Stability of implanted material is important not only for a stable function, but also because degradation products may be harmful to the host organism. Overview about biological reactions to implanted materials can be found in (69).

Chemical biocompatibility

Chemically appropriate implant materials are designed to be as inert as possible. If chemical reactions are to be expected they should be minimal and all resulting products should be inert. Candidate materials for neuroprothesis pass especially rigorous testing since they must remain inert not only passively but also when subjected to electrical stimulation. Typical materials for nerve electrode arrays include platinum-iridium alloys or stainless steel for the conducting parts and epoxy resins, polytetrafluoroethylene (PTFE, Teflon®), silicone rubbers, and polyimide for insulators (29,70). These polymers are biocompatible, electrically insulating and stable.

The amount of Pt ions released into the surrounding tissue may be neglected even after long-term stimulation. During the last years, Ir has been of increasing importance because a stable oxide film can be formed on the surface of Ir electrodes. This oxide film has a big charge delivery capacity and is, for this reason, well suited for stimulating electrodes. Pt and Ir are established materials in microelectronics, and carbon can be deposited onto microelectronic structures. Glassy carbon or carbon fibers are also used as electrode materials, and they are biocompatible and stable, though they have a higher roughness than metals. The bulk properties of polymers as backbones for electrodes can be modified to a certain degree and also surface modification procedures are performed in order to improve biocompatibility. However, certain surface modifications like autologous protein coatings also enhance the adhesion of pathogenic bacteria to the implant surface (71,72). A review on the chemical modifications employed in the production for neural prostheses can be found in (29).

Mechanical biocompatibility

The mechanical biocompatibility of an implant depends on the basic mechanical properties of the tissue and the implant. Ideally, the implantable device should have mechanical properties similar to the tissue in which it is implanted. This includes flexibility, strength and durability. It is also important to consider the tissue motion within the implantation site. For example, flexibility is important in the peroneal foot-drop stimulator and not in the devices for spinal cord stimulation and anterior lumbo-sacral root stimulation. For any implant, the allowable size must be defined relative to its function. It is not necessarily true that increased function is associated with larger size. The geometrical characteristics of an implant are of great importance too. For example, sharp edges and blunt corners should be avoided. The primary goal for a cuff electrode design is to minimize the size, as any constriction injury in the implanted site should be avoided. Such designs have been associated with incidence of morphological changes in neural tissue like axonal degeneration, demyelinization and fibrosis (37). Thus, the recommendation had been to implant cuffs with an internal diameter equal to 150% of the nerve diameter (73). However, this recommendation was criticized as to be actually more likely to create neuronal trauma (37). It also limits the degree of selectivity that is obtained during extraneural stimulation (31,41).

Implantation and nerve damage

The key factor determining the damage of electrode implantation is the disruption of the microcirculation of the nerve, which results in edema. This holds especially for intrafascicular electrodes. Another factor is the damage to the endoneurium and the disruption of the homeostasis, maintained by the blood-nerve barrier. The mechanisms of the damage during implantation are still debatable. According to Agnew and McCreery (70) on the first place stands direct mechanical interaction between the electrode and the nerve. Other mechanisms that may play a role during implantation are:

- *Surgical trauma to either the neural microvasculature or the nerve itself.*
- *Pressure caused by post-surgical edema, seroma formation, or excessive fibrous encapsulation of the implant.*
- *Reduced mobilization of the nerve caused by excessive scar tissue formation, which could fuse the nerve to the surrounding tissues.*
- *Undue tension in the electrode leads.*
- *The transmission of forces from muscles to the electrode array and the nerve.*
- *Obstruction of the microcirculation.*

For epineural and intraneural designs in particular, the most important factors are the implant procedure itself and transmission of tension *via* the leads.

Tissue reaction to implantation

Implantation usually causes foreign body reaction involving the natural inflammatory defensive response of the body. The acute response starts with protein adsorption onto the

surface of the implant. Therefore, the surface properties like roughness and surface chemical composition, which depend on the production process, are important for the grade of the subsequent response (74). The late response produces the typical cellular and humoral reaction including tissue edema, cytokines secretion, neutrophil, lymphocyte and macrophage migration and adhesion. This is a complex process mediated by the secreted cytokines.

The chronic reaction includes formation of a fibrotic capsule around the foreign body that consists of collagen fibers and fibroblasts. The thickness and the structure of the capsule are generally a measure of the severity of the response. The severity of the reactions can be determined by the amount of the giant Langerhans cells and macrophages. The electrical properties of this fibrotic capsule were studied by Grill and Mortimer (75). They found that the resistivity of the encapsulating tissue had a frequency dependency between 10 Hz and 1 kHz and decreased from 454 ± 123 to 193 ± 98 Ω.cm. It was frequency-independent between 1 kHz and 100 kHz with a mean value of 195 ± 88 Ω.cm. Moreover, the fibrotic capsule may lead to displacement of the electrode positions and changes in the tissue impedance (75).

The results from early experiments (37,76) indicated that nerves implanted with snuggly fitting spiral cuffs showed signs of sustained trauma. The typical pattern was a crescent-shaped region containing thinly myelinated axons, proliferation of subperineurial connective tissue, and a reduced axon density. In a more extensive study of the tissue reaction to the spiral cuff, 4 out of 44 nerves exhibited peripheral crescent-shaped areas, which contained thinly myelinated fibers with an apparent reduction in axon density, but there was no correlation between the cuff-to-nerve diameter ratio and the presence of morphological abnormalities. Similar results have been obtained in cuff electrode studies (77). Recently, Grill and Mortimer (78) reported focal areas of abnormal neural morphology including perineurial thickening, endoneurial fibrosis, thinly myelinated axons, and focal reduction in the density of myelinated axons in chronic implantation experiments with cuff electrodes.

Intrafascicular electrodes can also produce morphological changes in neural tissue (63). Chronic implantation of intraneural coiled-wire electrodes showed endoneurial fibrosis and edema, loss of nerve fibers with the large myelinated fibers being the most susceptible, and variable shifts in the excitation threshold. However, there were no changes in conduction velocities indicating that no significant damage occurred due to implantation. (61). The bulbous enlargement formed at the point where the electrode penetrated the perineurium was associated with focal nerve fiber compression, demyelination, edema, and fibrosis (61,79). Electrodes sutured to the epineurium have also led to neural damage including endoneurial edema, endoneurial fibrosis, loss of axons, and reduction of myelin (80,81). In general, intraneural electrodes are associated with a greater risk of trauma than the cuff-electrodes (82).

Nervous tissue reaction to electrical stimulation

Brief stimulation of the peripheral (83) or the cranial nerves results in increased expression in the neuronal cell body of immediate early genes (IEG) such as *c-fos* (84). The IEG family consists of approximately 30 members, whose product proteins act as transcription factors (85). These molecules are typically activated shortly after cell stimulation, without a requirement for *de novo* protein synthesis. Brief unilateral electrical stimulation of the cochlear nerve (120-250 μA, 5 Hz, 30 min) in anaesthetized rats with a biphasic current resulted in increased expression of *c-fos* in the ipsilateral ventral and bilateral dorsal cochlear nucleus (84). Intracochlear electrical stimulation with a cochlear implant in rats lead to changes in the phosphorylation state of the cAMP response element binding protein (CREB) and the expression of c-*fos* and *egr-1* in a tonotopically precise pattern in the central auditory neurons (86), which reside in nearly all auditory brainstem nuclei. Moreover, effects of electrical stimulation were identified in the medial vestibular nucleus and the lateral parabrachial nucleus. Regionally, CREB was dephosphorylated, wherever IEG expression went up. These massive stimulation-dependent modulations of transcription factors in the ascending auditory system indicate ongoing plastic changes as a consequence of the stimulation of the inner ear.

In the spinal cord, Molander *et al* (87) showed that in chronically axotomized nerves, *c-fos* is expressed after electrical stimulation of the fibers. Stimulation of the normal sciatic nerve at C-fiber intensity resulted in c-Fos-positive cells within the sciatic projection territory in the ipsilateral dorsal horn (lamina I and outer lamina II) and stimulation of A/B fibers had little effect. The expression was delimited to the projection areas of the sensory A/B-fibers (ipsilateral laminae II, III and IV and in the gracile nucleus) in young animals. This suggests that the excitability of these neurons is increased by nerve injury.

The role of the IEG is implied in the structural plasticity of the nervous systems (88,89). One may speculate that the continuous improvement of the responses of the individuals after early rehabilitation, in contrast with late rehabilitation, is due to FES guiding the plastic phenomena occurring after injury in a direction towards restoration of function. This line of thought is supported also in the review on animal experimentation (90) showing accumulation of physiological and behavioral data that adaptive (plastic) processes also occur within spinal circuits. The potential ability of the spinal cord to "learn" has obvious implications for altering and improving locomotor function after injury. Recent studies in man indicate that a significant population of stroke and spinal cord

injury (SCI) patients could also benefit from FES rehabilitation (91,92). In particular, it was found that stroke patients as well as incomplete SCI patients subjected to intensive FES treatment were able to recover grasping or walking function faster and better compared to patients who did not participate in the FES treatment post injury.

In the peripheral nervous system, prolonged high-frequency (>20-50 Hz) electrical stimulation of a peripheral nerve induces a typical type of neural injury, called early axonal degeneration, with a characteristic "salt-and-pepper" like mixture of "normal" and damaged fibers. The primary damage is observed as collapse of the myelin into the axoplasm and is restricted primarily to the large caliber axons (Aα, Aβ type). It is followed by degradation and phagocytosis of the axon (77,82,93). The neuronal injury originating from electrical stimulation has two mechanisms of occurrence:

- *Direct injury* resulting from the electrochemical process near the electrodes. Brummmer and Turner (94) have shown that the rate of production of compounds by electrochemical reactions and the type of compounds produced are directly related to the charge density (charge transferred per unit area of the electrode surface). The charge density near the surface of an electrode determines the extent of depolarization and hyperpolarization induced in the neurons close to the electrodes. If such depolarization is abundant and going on for a long time, the second mechanism of injury comes into play.
- The *excitotoxic neuronal injury* is caused by the excitatory neurotransmitter glutamate through its NMDA receptors. Thus, MK-801, a potent NMDA receptor antagonist, is a neuroprotective factor during prolonged electrical stimulation (95). The mechanism of the induced neuronal cell death is necrotic. Such damage occurs when the stimulus charge density or the charge *per* phase are large.

Selectivity concepts

In the paradigm of the implantable devices, selective stimulation of individual components of multifascicular nerves would allow control of several muscles with less hardware (43). Different aspects of selectivity may be distinguished depending on the structures being stimulated. Here we propose modification of the classification of Smit (55).

- *Muscle selectivity* is the possibility to activate any specific muscle by peripheral nerve stimulation. This implies stimulation of only a particular part of a (peripheral) nerve. In other words, it implies control at the level of the individual muscle.
- *Spatial selectivity* is the possibility to stimulate a particular region inside a nervous structure.
- The peripheral and the spinal nerves generally consist of several morphologically distinct suborgans, called fascicles. Therefore, a suitable definition of *fascicle selectivity* is the stimulation of only one fascicle in a multifascicular peripheral nerve without spread of the activation to other fascicles. It is a special case of spatial selectivity.
- *Fiber selectivity* is another special case of the spatial selectivity. It can be defined as activation of single nerve fibers.
- The nerves consist of axons, which in general have different sizes. Usually the fiber size distribution is multimodal. *Size selectivity* can be defined as activation of fibers of a particular size group.

Surface stimulation versus *implantation*

An important advantage of the surface FES systems is that they do not require surgical intervention, with its inherent risks. They also can be removed at any time if contraindications arise. Another advantage is that the transcutaneous electrode can be placed directly above the target muscle, and thus muscle-selective stimulation can be achieved (96). A typical example where surface stimulation can be used is the restoration of hand function. Surface FES can be applied at a very early stage of the rehabilitation, during the recovery and reorganization period of the central and peripheral nervous systems (plasticity), allowing early benefit for the patient. FES training during recovery may help a subject to restore a function to the point that he/she no longer needs a neuroprosthesis.

Popovic *et al* (91) advocate an early start of FES as part of the rehabilitation in stroke patients. This benefits the use of surface FES systems since the objective of the treatment is to help patients to relearn the grasping task rather than to provide them with a permanent assisting system. In SCI subjects there are two possibilities: implantation and surface stimulation. For the implantation, the patient should have reached stable neurological status. Surface FES is also preferred in treatment of spasticity in order to strengthen the antagonistic muscles and in recovery of simple movements, which requires stimulation by few electrodes with easy positioning (4). A disadvantage is that only a small part of a muscle can be stimulated, causing a rapid development of muscle fatigue. Furthermore, the reproducibility of muscle force is insufficient due to changes in the muscle geometry during contraction. Another issue is the displacement of the electrodes, which may occur during use of the FES device (96).

The advantages of the implantable FES systems are that the stimulation does not depend on the geometry of the muscle and a single electrode can stimulate several muscles with low energy consumption. Therefore, implantable stimulation is preferred in the following cases (4):

- When *deep muscles* that are difficult to stimulate by

surface electrodes have to be recruited.
- For *complex movements* which require a large number of electrodes in a limited space.
- To avoid *pain and burns*, caused by stimulation of the pain receptors and the skin.

The disadvantages are that the existing implantable FES systems still do not provide enough selectivity of stimulation, the surgical trauma associated with the implantation and some unresolved issues in the geometry of the electrodes (97). In conclusion, the implantation of a FES device causes acute, late and chronic inflammatory responses. The smallest effect is caused by the chemical reaction due to the inert materials used for the implantable parts production. The largest damage comes from the mechanical stress during movement or is due to the surgery.

CURRENT CLINICAL APPLICATIONS OF FES

The cochlear implant

The cochlear implant relies on the assumption that there are enough auditory nerve fibers left for stimulation near the electrodes. Although the first fully implantable cochlear prostheses preceded the fully implantable heart pacemakers, in the 1970s, heart pacemakers achieved high reliability and improved quality of life of the patients. In the USA, FDA nevertheless approved the first cochlear implant device for clinical use not earlier than 1984. Over the past 20 years of clinical experience more than 20,000 people worldwide have received cochlear implants.

Cochlear implantation has a profound impact on hearing and speech perception in postlingually deafened adults. Most individuals demonstrate significantly enhanced speech reading capabilities, attaining scores of 90-100 percent correct on everyday sentence materials (98). Moreover, according to the NIH Consensus Statement, the cochlear implant is the first, and still the only, neural prosthesis that is aiding a significant portion of a disabled population. In recapitulation - while the cochlear implant has reached wide acceptance and maturity as device, most of the other neuroprosthetic applications are still in their childhood.

Drop-foot stimulator

The first neuroprosthesis for walking was developed in 1961 by Liberson and colleagues (15). This system was developed to compensate for the "drop-foot" problem. The drop-foot is a pathological condition, caused by diminished ability to use the muscles that lift the foot. It may be caused by stroke, cerebral palsy, multiple sclerosis or neurological trauma. By stimulating the peroneal nerve, the prosthesis elicited ankle dorsiflexion, eversion and/or inversion thus allowing the subject to make a step with the disabled leg. Since then, a multitude of devices has been developed, mostly in former Yugoslavia. The Fepa system was proposed by Vodovnik and colleagues (99). Currently there are several commercial systems all based on surface stimulation - MikroFES (Jozef Stefan Institute of Science, Slovenia), Odstock 2 (Salisbury District Hospital, UK) (100) and WalkAide (Neuromotion, Canada) (101). The drop-foot stimulators are commonly controlled by a foot switch. A recent overview on the different FES systems can be found in Popovic *et al* (97). Thus far, most systems are external with a surface electrode placed over the peroneal nerve just below the head of the fibula.

More recently, radio-frequency transmitter enabled implants have been developed: for example, the new implantable two-channel system (Finetech, UK) (102) with subepineural electrodes in the *n. peroneus profundus* and *n. peroneus superficalis*. By 2002, it has been tested in 10 patients. It has the ability to stimulate independently the deep and superficial branch of the peroneal nerve, thus allowing the correction for excessive eversion and inversion (Fig. 6).

Odstock 2 is a surface stimulation system that has been used mostly in the clinical environment. It is based on the stimulator proposed by Liberson. The device can be used as an assisting aid or as a training device to strengthen muscles and improve voluntary control. Additionally, the device has a role in physiotherapy in gait re-education allowing isolated components of the gait cycle to be practiced under a therapist control (103,104). The Odstock 2 was perceived by the users to be of considerable benefit. A comprehensive clinical follow-up service is essential to achieve the maximum continuing benefit from FES-based orthoses. A recent review on the subject can be found in (97,105). Odstock 2 and the MikroFES, have been applied to more than 500 subjects. However, thus far, only the WalkAid has been FDA approved.

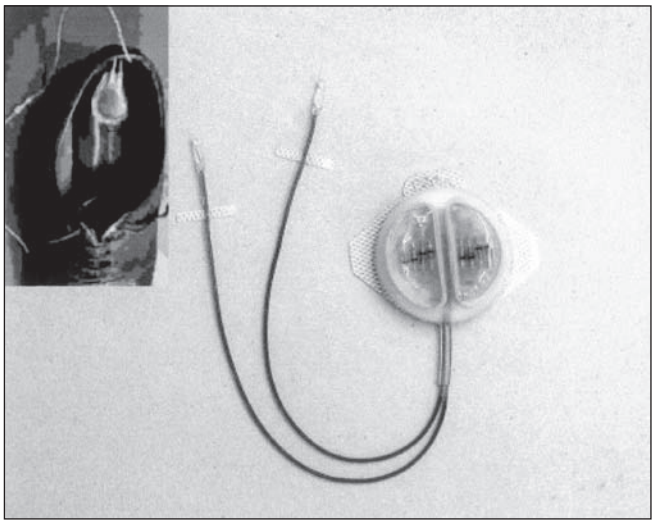

Figure 6. *The peroneal stimulator (Finetech, UK). This dual channel implant will soon be registered with CE mark. Courtesy: G. Bulstra and H.E. van der Aa.*

Restoration of lower limb function

In 1963, Kantrowitz reported the first application of FES to a T3 paraplegic patient who achieved standing by surface stimulation of the gluteus and the quadriceps for brief periods. The first systems were external devices enabling walking and were developed by Bajd and Kralj in the 1970s through 1980s in Lublijana, Slovenia (106). The initial devices only used two surface stimulation channels for each leg to produce standing and walking. The stimulation was delivered to both knee extensors. Devices with 4 channels have been proposed later (107). Systems used by patients included stationary bikes for exercise, transfer systems to enable the patient to move between a wheelchair and a bed, transfer systems between standing and sitting, and walking aids (106). The targeted patient group was paraplegics after SCI. Patients used a rolling walker frame or crutches for support. About 50 patients successfully used the system (108). One of the first implantable multichannel stimulators was developed by Brindley with electrodes applied on the femoral and the gluteal nerves (109). An overview of the contemporary devices can be found in (97). In brief, they are Parastep, LARSI (110), FESmate, HAS, RGO, Praxis24, and the implanted FES system proposed in (111).

The only commercialized system, developed initially by Graupe and colleagues (112,113) is Parastep (Sigmedics Inc., USA). It is based on the earlier work of Kralj (106). The target patient group consists of the complete or almost complete T4-T12 SCI patients. The system uses surface electrodes and no orthotic aids. The Parastep system was applied to more than 400 subjects and was the first FDA-approved FES system. Although FES of locomotion gains clinical acceptance, it is still in its experimental phase of development. At this stage, FES of locomotion is so far incapable to deliver a complete treatment for the target groups of patients. Only in several cases, it may provide pathogenetic treatment. The main impediment of its development is the insufficient selectivity of stimulation and the small number of applications in patients, which hinders assessment of any beneficial clinical outcome.

Hand disabilities - reaching and grasping

In tetraplegic and stroke patients, the most important target for achieving a high level of independence in active daily life is the restoration of the hand function. Thus, the main objective in applying FES to such patients is to improve the hand function by creating a reliable and long lasting power grasp, or a smooth pulp-pinch grasp that is needed to manipulate small objects. Neuroprostheses for grasping are used to restore or improve grasping function in tetraplegic and stroke subjects. The patients that would benefit most from such a neuroprosthesis would be the C5-C7 quadriplegics. The available neuroprostheses for grasping enable the restoration of the two most frequently used grasping styles, the palmar and the lateral grasp (114). The best known grasping neuroprostheses are the Freehand system (115), Handmaster NMS (116), Bionic Glove (117), NEC FESMate system (118), ETHZ-ParaCare neuroprosthesis (114), the systems developed by Rebersek and Vodovnik (119) and the Belgrade Grasping system (120). A recent overview can be found in (91).

In 1997, FDA approved for clinical use the *Freehand* system (NeuroControl Corp., Cleveland, Ohio) for restoration of the hand grasp in quadriplegics. The research and development process took 25 years, mostly carried out by the researchers at the Case Western Reserve University. The device consists of a stimulator and electrodes implanted in wrist and forearm muscles, a "joystick" controller implanted in the opposite shoulder, and an external processing unit (115). The joystick-like sensor placed on the chest relaxes and tightens the hand as the shoulder moves back and forth. A detailed description of the prosthesis can be found in (121). This prosthesis has been experimentally implanted in more than 130 people. With training, most patients with this device can open and close their hand in two different grasping movements and lock the grasp in place by moving their shoulder in different ways. A recent small clinical study with 6 patients in Australia (122) is a sign of increasing acceptance and application of the Freehand system outside USA. The researchers reported that all subjects were able to grasp, move and release more objects within the 30-second test period with the neuroprosthesis than without it. In 85% of the occasions, the six subjects expressed a preference for using the neuroprosthesis to perform these activities in daily living. Twelve months after rehabilitation, five of the six subjects still used the neuroprosthesis regularly. One of the main advantages of the Freehand system is that the time needed to put on (donning) and to take off (doffing) the system is significantly shorter compared to most surface stimulation FES systems. On the other hand, the Freehand system can be applied only 18-24 months after the injury and is only suitable for SCI subjects and not individuals suffering from stroke (114).

The *Bionic Glove* is a hybrid system that utilizes a glove with FES electrodes. The detection of wrist extension stimulates finger flexion; therefore, the control of the device is directly related to the normal grasping sequence. Only patients who have sufficient wrist extension strength can use this type of device. The controls of the Freehand system and the Handmaster are not related to the normal movements included in the motor function, whereas the Bionic Glove uses mechanical sensors to detect wrist extension and the control is therefore directly coordinated by the grasping sequence. Reported as a part of a multicenter clinical trial, Bionic Glove could significantly improve independence in patients with C5-C7 spinal cord injury.

The *Handmaster* is an orthosis for grasping with three

pairs of surface stimulation electrodes. This system can be used to generate a grasping function in tetraplegic and stroke patients. Originally, this system was envisioned as an exercise and rehabilitation tool, but it is also used as a permanent prosthetic system. One of the advantages of the Handmaster is that it is easy to put on and to take off. The Handmaster is predominately used as an exercise tool for stroke subjects and is commercially available in a limited number of countries.

An interesting attempt is the *MeCFES* system (myoelectrical controlled functional electrical stimulator) where the residual myoelectric signals from the paretic wrist extensor (*m. extensor carpi radialis*) are used to control stimulation of either the wrist extension (i.e., the same muscle) or thumb flexion. Initial results of six spinal cord lesion patients and one stroke patient show improvement of the wrist extension (124). With the exception of the Freehand and MeCFES systems, all other neuroprostheses for grasping are FES systems with surface stimulation technology. Only the Freehand and Handmaster systems are currently available on the market while the other neuroprostheses are produced in laboratory environments.

All of the discussed neuroprostheses for grasping have demonstrated, in clinical trials in stroke and/or SCI subjects, improvement of the grasping function. These systems confirmed that the FES technology in principle could facilitate comfortable and secure grasp. However, the grasp strategies that can be provided with the existing neuroprostheses for grasping are very limited and can only be used for a restricted set of grasping and holding tasks. Thus, it is too early to consider as a success any of the existing systems, including Freehand and Handmaster, because of the small number of patients using the systems (about 150 for Freehand and a comparable number for Handmaster).

Phrenic stimulation

Of those patients who sustain a high cervical spinal cord injury, a substantial number initially require some form of mechanical ventilation of their lungs. Most of them are able to breathe spontaneously with recovery, but 25% remain dependent upon some form of ventilation support for the remainder of their lives. Most of these injuries occur in young, otherwise healthy people with a life expectancy of 20 years or more, assuming they have access to appropriate medical care. In patients with cervical lesions of the spinal cord, direct stimulation of the phrenic nerve can be applied for respiratory pacing. This is one of the earliest clinical applications of FES.

Diaphragm pacing is useful for conditions in which the brain stem respiratory centers provide little or no activation of the respiratory muscles, i.e. central hypoventilation syndrome, Arnold-Chiari malformation/brain stem dysfunction and high quadriplegia. Suitable patients are those with an intact phrenic nerve motor neuron pool in their cervical spinal cord on both sides. This can be checked by measuring the phrenic nerve conduction velocity and the diaphragm electromyogram. To accomplish this, phrenic nerves are stimulated by needle or surface electrodes in the neck, and the diaphragm muscle electromyogram is recorded from electrodes placed low on the chest at the front. The patient wears an external radio-frequency transmitter over an implanted receiver, and a stimulating current is induced without the need for any percutaneous wires. The introduction of phrenic nerve pacing more than two decades ago by Dr William Glenn and associates at Yale University has provided many ventilator-dependent tetraplegic patients with freedom from mechanical ventilation (9,125,126).

More than 1,200 phrenic nerve stimulator implantations have been performed throughout the world since 1968. Patients from several months to over 80 years of age have been successfully implanted and paced for more than 10 years. The longest period of pacing in a patient has been more than 20 years. In patients with ventilator-dependent quadriplegia, phrenic nerve pacing provides significant clinical advantages compared with mechanical ventilation. This technique, however, requires a thoracotomy with its associated risks, in-patient hospital stay, and some risk of phrenic nerve injury.

During the past decade, diaphragm pacing has also been attempted in small infants. The appropriate stimulation parameters are low stimulus frequency, short inspiration time and moderate respiratory rate. In a clinical trial in 33 pediatric patients, the mean time to failure was 56 months, which is acceptable for the limited application of the pacemakers (127). Among the benefits of the phrenic nerve pacing, the following can be outlined:

- Increased *mobility* of the patients.
- Improved *speech*.
- Improved *sense of well-being* and reduced anxiety due to elimination of fear of ventilator disconnection, elimination of ventilator tubing, elimination of ventilator noise, more physiological breathing and tracheostomy closure in some patients.
- Reduced incidence of *respiratory tract infections*.

In conclusion, one may consider the phrenic stimulator as a major improvement of the quality of life of the patient, which also reduces the total costs for nursing of the patient.

EVIDENCE-BASED EVALUATION FOR THE FES APPLICATIONS

Efficacy of FES after stroke

Meta analysis showed that in post-stroke hemiparetic patients FES promotes recovery of muscle strength if included as part of the rehabilitation. The study was based on the results of clinical trials dating between 1978 and 1992 (128). Further evidence suggests of improvement of the motor control of the upper extremity after stroke (129). The meta analysis was

based on six randomized controlled trials on the therapeutic electrical stimulation on motor control and functional abilities. After stroke, up to 81% of the individuals develop shoulder subluxation, a condition frequently associated with poor upper limb function. FES on the shoulder muscles has been used in treatment of this condition. The results of seven (four early and three late) trials indicate that when added to conventional therapy, FES is beneficial early after stroke for prevention of shoulder subluxation (130). Burridge *et al* (100) in a randomized controlled trial in subacute single stroke patients measured the effect of the Odstock Dropped Foot Stimulator as a supplement to physiotherapy. The results of 32 subjects showed an increase in walking speed and beneficial Physiological Cost Index with the use of the stimulator.

Efficacy of FES in urological conditions

Stimulation of the sacral spinal nerves or the sacral spinal roots or the pelvic nerves can be used to restore bladder function in patients with voiding disorders. Several therapeutic techniques have become established in clinical urology as part of therapy at an increasing number of specialized centers.

As part of the treatment of different kinds of lower urinary tract dysfunctions, refractory to conservative treatment, Tanagho and Schmidt introduced *sacral nerve neuromodulation* in the 1980s (131). Neuromodulation is now carried out by stimulation of the S3 sacral nerve. In brief, an electrode is placed in S3 foramen. The electrode has to be brought into the ventral side of the opening in front of the S3 ventral ramus. This procedure is minimally invasive, as compared to sacral neurostimulation. The patient is sent home with an external pulse generator for a few days as part of an evaluation test. Responders are then implanted with a permanent sacral foramen implant and an implantable pulse generator (132). Since its early applications, neuromodulation has grown in popularity and the indications for this procedure are multiplying. Among them are *urge incontinence* and *sensory urgency, idiopathic chronic urinary retention, pelvic pain* and *interstitial cystitis* (133). Complications in general are minimal - electrode migration, electrode failure and pain at the implantable pulse generator site (134).

The *sacral neurostimulation* approach proposed in the 1980s by Brindley (135) consists of intradural implantation of a so-called book electrode to stimulate S2-S3 ventral roots, together with posterior S2-S4 rhizotomy. The primary purpose of the Brindley bladder stimulator is to improve bladder emptying, thereby eliminating urinary infection and preserving kidney function in suprasacral SCI patients. It also assists in defecation and enables male patients to have a sustained full erection. Nowadays, the Brindley bladder stimulator is being developed by the company Finetech in UK.

The suprasacral SCI patients develop *detrusor sphincter dysinergy*, which imposes serious health risk. The results from the first 500 patients implanted with the Brindley stimulator show usage in 424 after a mean follow up of 4 years (136). Another study reported 38 patients with a complete spinal cord lesion (137). During the follow-up period, ranging up to 12 years, all patients had an increased bladder capacity and reduced residual urine volumes, 31 patients were continent, 29 males could achieve a sustained full erection, 27 patients used the implant for bowel function. The long long-term favorable effects of the stimulator were also confirmed in follow-up studies on urodynamics (138) and cost-effectiveness (139) in 52 patients.

The *overactive bladder* comprises a spectrum of conditions ranging from urgency-frequency syndrome to urge incontinence. The incidence of the overactive bladder increases with age, with a prevalence ranging from 4% to 5.5% of the population. The efficacy of the neuromodulation therapy was evaluated in a prospective 12-center study in Europe, Canada, and the United States conducted form 1993 to 1999 with the InterStim system (Medtronic, Inc., Minneapolis, Minnesota). The study enrolled 184 patients for urinary urge incontinence, 220 for urgency-frequency, and 177 for retention for a total of 581 patients (140).

Neuromodulation is used for patients with *urge incontinence* and with therapy-resistant idiopathic *detrusor instability*, where in a follow-up trial results showed clinically significant improvement of the quality of life (133). In patients with detrusor hyperactivity implantable neuroprosthetic devices also lead to improvement in the urodynamic parameters (141). Out of 20 patients with urge urinary incontinence, presented by Thon and colleagues (142), 17 showed an improvement of more than 50% compared to the baseline, which persisted for more than one year of follow-up. Elabbady and colleagues (143) presented their results in 9 patients with urgency frequency and/or urge incontinence: frequency improved by 73%, urgency by 42% and incontinence by 50%. However, the number of patients is small to derive statistically valid conclusions for the success rate of the operation. On the other hand, the outcome of the multi-center trial is promising. Results demonstrate that after 3 years, 59% of 41 urinary urge incontinent patients showed greater than 50% reduction in leaking episodes *per* day with 46% of patients being completely dry. After 2 years, 56% of the urgency-frequency patients showed greater than 50% reduction in voids *per* day (140).

Results for the *idiopathic non-obstructive chronic urinary retention* of a multi-center trial were also separately reported (144). A total of 177 patients with urinary retention refractory to standard therapy were enrolled in the study. Compared to the control group, patients implanted with the InterStim system had statistically and clinically significant reductions in the catheter volume *per* catheterization. Successful results

were achieved in 83% of the implant group with retention compared to 9% of the control group at 6 months. Temporary inactivation of sacral nerve stimulation therapy resulted in a significant increase in residual volumes but effectiveness of sacral nerve stimulation was sustained through 18 months after implant. In another study, Thon and colleagues (142) reported that from 33 patients with chronic urinary retention implanted permanently with neuroprosthesis 23 showed a long-lasting significant improvement, but in the remaining 10 the improvement did not reach 50% compared to baseline. In 7 patients with chronic retention, Vapnek and Schmidt (145) reported for success in 5 cases and Elabbady and colleagues (143) presented success in 8 of 8 cases. Results of all the presented studies demonstrate that sacral nerve stimulation is effective for restoring voiding in patients with retention who are refractory to other forms of treatment.

Pelvic pain or *discomfort* is a very common symptom associated with other storage or voiding dysfunctions. In the available literature on sacral root neuromodulation, associated pelvic pain has improved from 85% to 90% when post-implant status was compared to baseline (134,142).

In conclusion, the correlation between the clinical outcome and the urodynamic test results is poor. The results of the presented studies on neuromodulation show that 40% of the selected patients do not qualify for the procedure and the effect of treatment is not enduring: voiding dysfunctions return as soon as the neuroprosthesis is switched off. It is thought that the effect is based on antidromic stimulation of the inhibitory neurons in the spinal cord. Due to the fact that the stimulators are voltage-controlled, the amount of injected current into the tissues is unknown, and the fibers (perhaps both myelinated and non-myelinated) that are stimulated are also not known, as well as the direction of stimulation (ortho- or antidromic). Additional basic and clinical research needs to be performed before this treatment can be introduced as a routine procedure in patients with serious voiding dysfunction refractory to conservative measures (146).

EXPERIMENTAL AND THEORETICAL RESEARCH

Experimental research

- *Visual prosthesis: blind eye versus normal brain*

Blindness can result when any step of the optical pathway - the optics, the retina, the optic nerve, visual cortex, or other cortical areas involved in the processing of vision - sustains damage. In Germany, 17,000 patients become blind every year for whom there is no effective treatment or cure (*1*).

Public discussion of the electricity effect on vision dates back to 1751, when it was addressed by Benjamin Franklin following his celebrated kite-and-key experiment. Despite some advocates, the idea of treating blindness through electrical stimulation did not catch on. In the last few decades, extensive experimental research for development of visual prostheses has been performed. In 1967-68, the experiments of Brindley and Lewin (14) showed the feasibility of the long-term interface with the visual system. The approach of the cortical prostheses has its foundations in the observations of the visuotopic organization of electrically evoked phosphenes in the occipital cortex. This have led a number of investigators to propose that electrical stimulation of visual cortex *via* arrays of electrodes might provide the profoundly blind with a limited form of functional vision. Several groups investigated the stimulation with cortical surface electrodes, the so-called "cortical prostheses" of Brindley (14) and Dobelle (147), the cortical penetrating electrodes of Bartlett and Doty (1980)(148), and the electrodes of Schmidt, and Hambrecht (1996)(149). However influential it is, so far this idea has very little practical progress. The neurons in the cortex recognize textures, depth (displacements), angles and brightness/color of the object. The perception of images is not based on pixelation, and therefore, all the bitmap-based stimulation approaches are doomed to fail. On the other hand, the cortical stimulation approach may provide the only therapeutic approach for individuals with non-functional retinas and/or optic nerves. Recently, Dobelle (150) reported the development of a visual prosthesis providing a sort of "artificial vision" to a blind volunteer by connecting a digital video camera, computer and associated electronics to the visual cortex of his brain. As an alternative to the cortical stimulation, two other approaches have also been investigated.

The idea to realize a visual prosthesis by *optic nerve stimulation* was conceived by Mortimer and Veraart (151) at the beginning of the 1990s. The first implantation was in 1998 and the patient was able to localize single bright spots of light, but high spatial resolution cannot be expected with such a stimulation arrangement. This prosthesis may show promise if an ultra-high electrode array count of intraneural electrodes are implanted in the optic nerve for providing better selectivity of stimulation. Although ingenious, so far the approach does not take into account the information processing steps taking places in the retinal ganglion cells.

At the end of the 1980s, an entirely new approach was undertaken by the teams of M. Humayun of John Hopkins University (149) and that of J. Rizzo of Harvard University (156), in association with the Massachusetts Institute of Technology. They developed an implantable electrode array for the retina itself, a *retinal implant*, in order to stimulate the retinal ganglion cells (152), which axons form the optic nerve. This prosthesis is referred to as "epiretinal implant". Another kind of retinal implant is the subretinal implant developed by Chow and colleagues (153) in Chicago, and Zrenner in Tubingen (154). Both teams (155,156), stimulated the retina of blind patients with epiretinal electrodes that were transiently inserted into the eye through a scleral opening.

The groups reported a sensation of light patterns by the patients, but perception of geometric patterns was reported in only a few instances. Recently, a permanent implantation has been made in a blind volunteer (157).

All results in the field in the past 30 years are still far from true object recognition. However, they do demonstrate the feasibility of generating perception of light patterns in blind people.

• *Spinal Cord Stimulation in motor disorders*

Apart from the pain suppression of chronic intractable pain, peripheral vascular disease and angina pectoris, spinal cord stimulation has been employed in motor disorders for control of spasticity in SCI patients. Attempts in this direction have been carried out for the first time in the 1980s by Richardson *et al* (161). Recently Pinter *et al* (162) stimulated the L2-L3 dorsal roots of the spinal cord in SCI patients. Results demonstrated reduction of the muscle hypertonia of the lower extremities.

A possible future application of spinal cord stimulation is to contribute to the restoration of the motor functions of the lower extremity (158,159). The reasoning behind this idea is that if we are able to control the Central Pattern Generator in the motor spinal cord, we circumvent many of the selectivity problems pointed out so far. There is accumulating evidence for the existence of a Central Pattern Generator of the locomotion in both primates and men (160). This requires a Multi Electrode Array to be placed on the spinal cord that should be able to stimulate the musculotopically-organized motor pools of the lower limbs.

Theoretical modeling studies

As part of the design of different types of electrodes for stimulation a substantial amount of theoretical and experimental research on selectivity has been performed. The electrical behavior of the myelinated nerve fiber can be represented by a simple cable network. The first to introduce this model was McNeal (27) in order to calculate how a stimulation-induced extracellular field affects nodal transmembrane voltages. According to this model, the node of Ranvier, which is closest to the cathode, will be excited first when the stimulus current is sufficiently high. The results of this theoretical approach are in accordance with the general observation that the threshold stimulus of a nerve fiber excitation is smallest near the cathode and rises with the increase of the distance (23).

• *Research on spatially-selective nerve stimulation*

The feasibility of selective activation of peripheral nerve fascicles was demonstrated by McNeal and Bowman (31), who found that with proper fit and positioning a single circumneural sleeve with multiple electrode contacts could control selectively the activation of two antagonist muscle groups innervated by a common nerve trunk. In their study, Sweeny *et al* (42) performed numerical modeling and experimental testing of a nerve cuff technique for selective stimulation of superficial peripheral nerve trunk regions. Two basic electrode configurations ("snug" cuff monopolar and tripolar longitudinally aligned dots) have been considered. Both modeling and experimentation suggested that longitudinally aligned tripolar dot electrodes on the surface of a nerve trunk would restrict excitation to superficial nerve trunk regions more successfully than monopolar dot electrodes. Transverse anodal "steering" improved the spatial selectivity of both monopolar and tripolar electrode configurations (42). With a sufficient number of electrodes within a so-called "cuff electrode", high selectivity of stimulation can be achieved by either longitudinal or transversal currents produced by appropriately switched electrodes (41).

Goodall *et al* (45) found that transverse current from an anode positioned opposite the stimulating cathode improved spatial selectivity, and position selectivity was enhanced when the ratio of transverse current to longitudinal current was increased. Based on computer modeling, Deurloo *et al* (44) concluded that transverse steering provides more selective stimulation than longitudinal steering (Fig. 7). Selectivity was dependent on the relative location of the electrode contacts and the nerve fascicles, as well as the size and relative spacing of neighboring fascicles (43). Deurloo *et al* (163) performed theoretical research on how to improve the selectivity performance of multi-contact cuff electrodes for stimulation of peripheral nerves. As the combination of controlled fiber size and spatial selectivity seems hard to achieve, the focus was primarily on spatial selectivity. They found that the transverse tripole is the only configuration that maximizes activation selectivity for a small (cylindrical) bundle of fibers in the periphery of a monofascicular nerve trunk (163) (see also Fig. 7). Inverse recruitment was less pronounced than for the other configurations. They recommended transverse tripolar stimulation since it did not change the shape of the recruitment contours, despite the lowering of the excitation threshold, which might occur in chronic implantation fibrosis on the implantation site. However, in acute animal experiments, where the recruitment characteristics of muscle selective nerve stimulation by a multi-contact nerve cuff electrode was studied, the results showed that only in a few cases transverse bi- and tripolar stimulation provided a better selectivity than monopolar stimulation (164). In accordance with the results of the modeling studies, bi- and tripolar stimulation required higher stimulus currents than monopolar stimulation, whereas maximum recruitment and slopes of recruitment curves were lower. Due to the variability in the number and size of the fascicles and their position in this nerve, sufficient reproducibility for the selectivity could not be obtained.

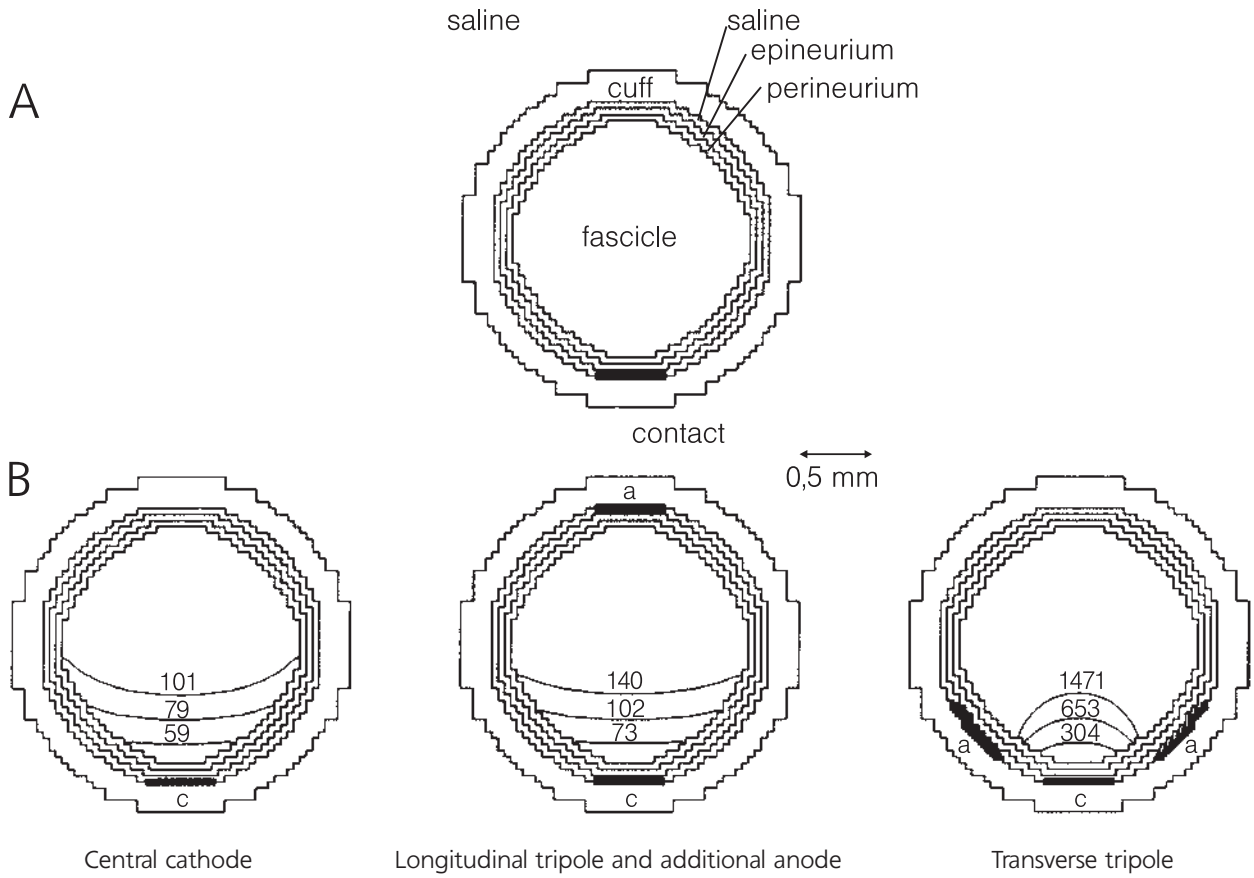

Figure 7. (A) *Transverse section of the 3D volume conductor model of a monofascicular nerve surrounded by an insulating cuff with an electrode contact on its inner surface.* ***(B)*** *Recruitment contours showing excitation regions in the nerve trunk. c - cathode, a - anode. Courtesy: K. Deurloo, from (96).*

The theoretical research performed by Rutten *et al* (56), and Yoshida and Horch (49) suggested that intraneural electrodes should give better spatial selectivity than cuff electrodes. In this line of reasoning, Rutten *et al* (165) argued that the best way to control individual fibers is to stimulate in close proximity of the nodes of Ranvier, which implies use of intrafascicular electrodes. However, the distribution of the nodes of Ranvier in the peripheral nerves makes the stimulation a probabilistic process. The experimental studies show that, despite the theoretical expectations, when the topography of the motor nerve fibers is unknown, the implanted intraneural electrode may simply miss the target fiber population. Several attempts for such stimulation have been made so far with 1D arrays. The obtained information gave insight on how to improve the design (the shape and distance between electrodes) of the later on produced 3D arrays.

In acute nerve implantation experiments, eight 5- to 24-wire-MEAs were used in order to investigate whether the electrodes could selectively stimulate single motor units. The results revealed partial blocking of neural conduction, similar to that reported with microneurographic insertion with single needle electrodes (166). The eight arrays were capable of evoking threshold forces selectively with an average efficiency of 81%. Frieswijk *et al* (167) performed animal experiments and model simulations of monopolar, intrafascicular nerve stimulation in order to study force-current relationships (recruitment curves). They found that the conductivity of the extraneural medium is of prime importance to the resulting recruitment curves: an insulating extraneural medium generally leads to steeper curves with lower threshold currents than a well-conducting extraneural medium. The statistical comparison of experimental and model results suggested clustering of the motor fibers, originating from a single muscle, within the same fascicle. This clustering manifested itself mainly by an increased spread in threshold currents, as opposed to the situation where the fibers are distributed

uniformly throughout the entire fascicle.

In conclusion, the insufficient neuroanatomical knowledge of the spatial organization and topography of fibers in the peripheral nerve hampers the definitive choice for the type and the design of the electrodes for functional stimulation.

- *Research on fiber size selective stimulation*

In myelinated axons, there is a positive correlation between the internodal distance and the axonal diameter. Thus, the large fibers (A, B) have nodes further apart than the small fibers. As a result, in an electric field, the larger fibers have a larger potential difference between adjacent nodes, leading to a lower threshold of the large fibers in comparison with the small ones. Therefore, during stimulation, the large myelinated fibers fire first. Unfortunately, this is the reverse to the natural order of recruitment, and it results in fast development of muscle fatigue. By activating/blocking stimuli delivered by multiple cuff electrodes the order of recruitment can be reversed, but yet the fibers can not be chosen (168). Better fiber size selectivity can be achieved by intraneural stimulation, as outlined by Rutten *et al* (165).

The order in which the nerve fibers in a peripheral nerve or a spinal root are excited by a stimulus pulse is predominantly related to both the fiber diameter and the distance between the fiber and the cathode (169). In the conducting media around the electrode, the current density is inversely proportional to 2^{nd}-3^{rd} power of the distance. Accordingly, the threshold current is increased at the same rate as shown empirically (23). In clinical applications, due to the generally limited amplitude range, only the large fibers will be recruited. For example in spinal cord stimulation, the maximal therapeutic amplitude should not exceed 170% of the paresthesia threshold perception. Calculations show that the nerve fibers smaller than 9 μm in diameter will not be recruited. Another relevant aspect of the recruitable large fibers is their density within the fascicle (169).

Fang and Mortimer (170,171) studied selective activation of small fibers without activating larger fibers in the same nerve trunk. In the proposed nerve stimulation system, quasitrapezoidal-shaped current pulses were delivered through a tripolar cuff electrode to effect differential block by membrane hyperpolarization. The quasitrapezoidal-shaped pulses with a square leading edge, a 350 microsecond(s) plateau, and an exponential trailing phase ensured the block of propagating action potentials and prevented the occurrence of anodal break excitation. The tripolar cuff electrode restricted current flow inside the cuff and thus eliminated the undesired nerve stimulation due to a "virtual cathode." The subsequent animal experiments confirmed that larger alpha motor axons could be blocked at lower current levels than smaller alpha motor axons, and that all alpha fibers could be blocked at lower current levels than gamma fibers, and the blocking threshold correlated with the fiber diameter (171). For the same purpose, van Bolhuis *et al* (172) suggested the use of two pulse generators independently supplying short supramaximal cathodal stimulating pulses (0.5 ms) and long subthreshold cathodal inactivating pulses (1.5 s) to the sciatic nerve. Results showed that propagation of action potentials was selectively blocked in nerve fibers of different diameters by adjusting the strength of the inactivating current (172).

Cathodal pre-pulses inverse the recruitment order (173,174). Grill and Mortimer (173) demonstrated that subthreshold membrane depolarization generated a transient decrease in neural excitability and thus an increase in the threshold for stimulation by a subsequent stimulus pulse. When a depolarizing stimulus pulse was applied immediately after the subthreshold depolarization, nerve fibers far from the electrode could be stimulated without stimulating fibers close to the electrode. Thus, subthreshold depolarizing prepulses allowed selective stimulation of nerve fibers far from the electrode. In a realistic model of a nerve fiber surrounded by a cuff electrode, Deurloo *et al* (174) showed that it is also possible to stimulate small fibers without exciting large ones. The applied model requires that, in the case of monopolar stimulation with a cuff electrode, the cuff length should not exceed twice the internodal length of the fibers to be blocked. Similarly, the distance between cathode and anode should not exceed the internodal length of these fibers when tripolar stimulation is used (174).

CONCLUSION

The principal requirements to any substituting structure are features mimicking some of the biological functions of nerves and replacing these functions depending on the scope of implantation. Profound knowledge about the development, functional and structural organization of the nervous system is a prerequisite for any attempt to establish meaningful recording or stimulation in order to substitute for a given function or modality. A number of proposed ideas for electronic implants are based, however, on a more "engineer-like" way of thinking rather than considering the complexity of the biological systems. The necessary for the engineering development reductionism approach often substitutes basic problems for secondary ones. For example, the concept of *spatial selectivity* in stimulation is often substituted for *fascicle selectivity*, which equalizes the fiber representation of a particular muscle contraction (dynamic view) to a coincidentally delimited anatomical region along the course of a nerve (static view).

During the last 50 years, a substantial amount of basic and applied research was performed in the field of FES, which

led to successful development of the cardiac and the phrenic pacemakers, and the cochlear prostheses. Nevertheless, a number of fundamental scientific problems still remain to be solved before we see a comparable degree of effectiveness and penetration in common medical practice for the contemporary locomotion neuroprostheses and urological FES appliances. Although FES of locomotion gains clinical acceptance, it is still in its experimental phase of development. There are several interrelated, but distinct, issues:

- Effectiveness and reliability of the devices
- Technical support
- The place of the devices in the complex treatments of neurological diseases, such as stroke, spinal cord injury, multiple sclerosis, etc.

Despite the significant technical progress achieved in the last 10-15 years in the FES field, there is a consensus that these systems are not sufficiently advanced and that they need further development. Complexity of human motion greatly diminishes the area of the animal experimentation in this field and puts the stress on computer modeling. Complexity makes the leap from a model to a patient even more difficult than from an animal model to human as seen in the performance of many implantable FES systems. Success has been achieved in a limited number of cases, diminishing the validity of the obtained results and leading to case descriptions rather than generalizations. This in turn increases the interval between trial and error (the most prominent approach in experimentation) and as a result slows down the research and development process for new applications. Nevertheless, the present FES treatments combined with conventional occupational and physical therapy still remain the most promising approach in rehabilitating spinal cord injury and stroke patients. The need of training, which is seen by some as a shortcoming of FES (97), in our opinion may be turned into advantage if it is integrated in the overall treatment and rehabilitation process.

The mechanism of action of electrical neuromodulation is still poorly understood, which leaves it in a rather empirical state of operation. Hundreds of patients have been treated successfully with the Brindley approach in bladder voiding disorders. However, the posterior rhizotomy, which is required, is a rather crude approach towards blocking the spinal reflexes. Nevertheless, FES is effective in improving the bladder function in the overactive bladder states and in spinal cord injury patients it gives long-term favorable results, which makes it a viable therapeutic option for the indicated groups of patients.

The research performed in the field of the visual prostheses showed the complexity of the information processing by the human visual system. Even the modest goals of the projects so far are ambitious compared with the information content of the reported visual phenomena. We would like to finish with a quotation from Dobelle (150), which applies to any prosthetic treatment: "*Development of implanted medical devices such as this artificial vision system progresses in three stages. First there is speculation, then there is hope, and finally there is promise.*"

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